

WOMEN WITH
BLEEDING DISORDERS
Module 2

Bleeding disorders in women: basic diagnosis and management

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What will you learn in this micro e-learning programme on women with bleeding disorders?

This micro e-learning programme consists of **two modules** aiming to increase awareness, knowledge, and understanding of bleeding disorders and their management among healthcare professionals who are the first to see women and girls with signs and symptoms of bleeding disorders.

Upon completion of the two modules, you will:

- Be able to **recognise the signs and symptoms** of bleeding disorders in women and be aware of their **impact on the quality of life** of women
- Know how to **identify women who are likely to have undiagnosed bleeding disorders**, initiate basic diagnostic testing, and arrange an appropriate referral for diagnosis
- Be able to **initiate management** of bleeding symptoms in women until specialist assessment is available

AFTER MODULE 2 YOU WILL:

Current Module

- **Understand the strengths and limitations of tests** used to diagnose bleeding disorders in women
- Be able to perform **basic interpretation of test results** to diagnose bleeding disorders in women
- Be able to **initiate management** of bleeding symptoms in women until specialist assessment can be performed

REFER TO MODULE 1 TO:

- Be able to **recognise the signs and symptoms** of bleeding disorders in women
- Be aware of the **impact on quality of life** of bleeding disorders in women
- **Know how to effectively screen for symptoms** of bleeding disorders in women by using the tools available

This micro e-learning module has been developed by a **multidisciplinary panel of experts**



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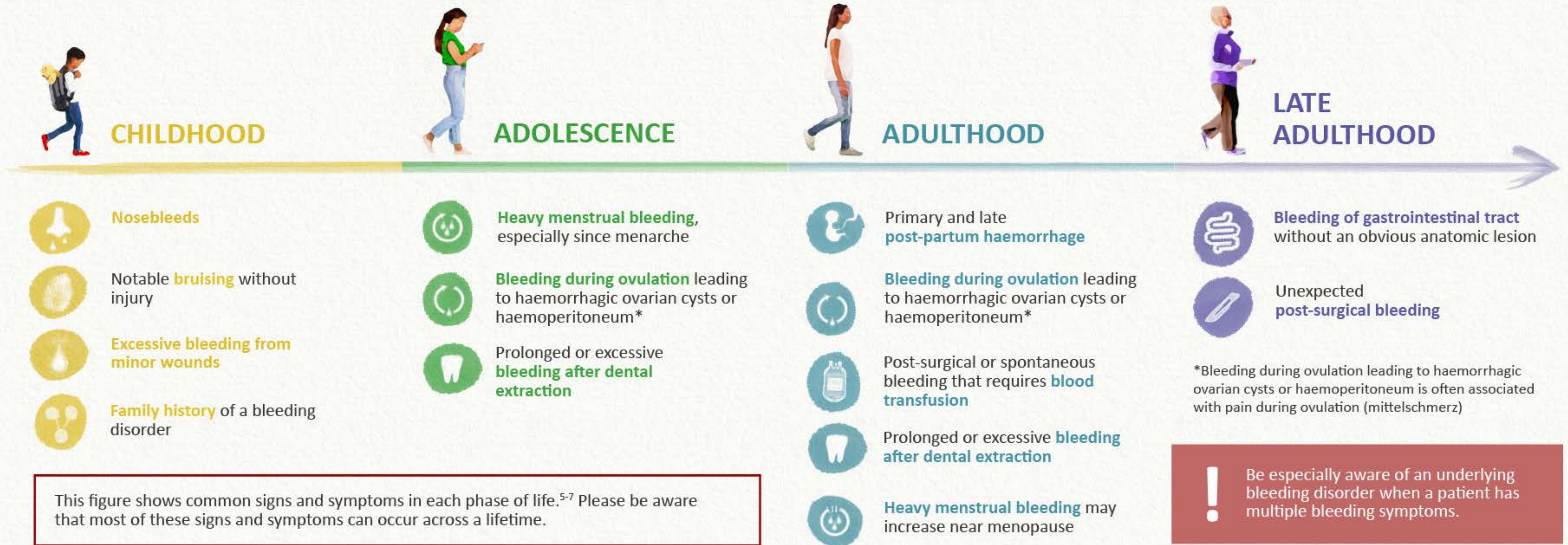
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When to suspect a bleeding disorder in women and girls

MODULE 1 SUMMARY

Module 1 of this micro e-learning programme described how **bleeding disorders occur as often in women as in men**, but women experience the additional bleeding challenges of menstruation and childbirth.¹⁻⁴

Despite the negative impact of these disorders on the quality of life and social participation of women and girls, there is a large diagnostic delay.



1. Kulkarni R. Eur J Haematol. 2015;95 Suppl 81:2-10; 2. Lavin M, et al. Blood Adv. 2018;2:1784-91; 3. Xu Y, et al. Haemophilia. 2017;23:115-21; 4. Noone D, et al. Haemophilia. 2019;25:468-74; 5. O'Brien SH. Blood. 2018;132:2134-42; 6. James AH, et al. Am J Obstet Gynecol. 2009;201:12.e1-8; 7. Philipp CS, et al. Obstet Gynecol. 2005;105:61-6

Next steps in women and girls with bleeding disorders

IN MODULE 1 WE LEARNED THAT IN WOMEN AND GIRLS WITH BLEEDING SYMPTOM(S):



The **personal bleeding history** should be assessed



The **family history** should be assessed



Several **tools** can be used to screen for a bleeding disorder

MODULE 2 DETAILS THE NEXT STEPS TO TAKE WHEN SUSPECTING A BLEEDING DISORDER



FIRST LINE

Perform general laboratory assessment and start symptomatic treatment



SECOND LINE

Contact a haematologist for diagnostic laboratory assessment and specialised management

! Note that if a patient has a known bleeding disorder, the patient's family members (men and women) should be screened by evaluating their personal bleeding histories and conducting laboratory assessment

FIRST LINE: perform general laboratory assessment if suspicion of a bleeding disorder is raised by personal bleeding history, family history, and screening tools

General assessments can be performed in first line



Full blood count

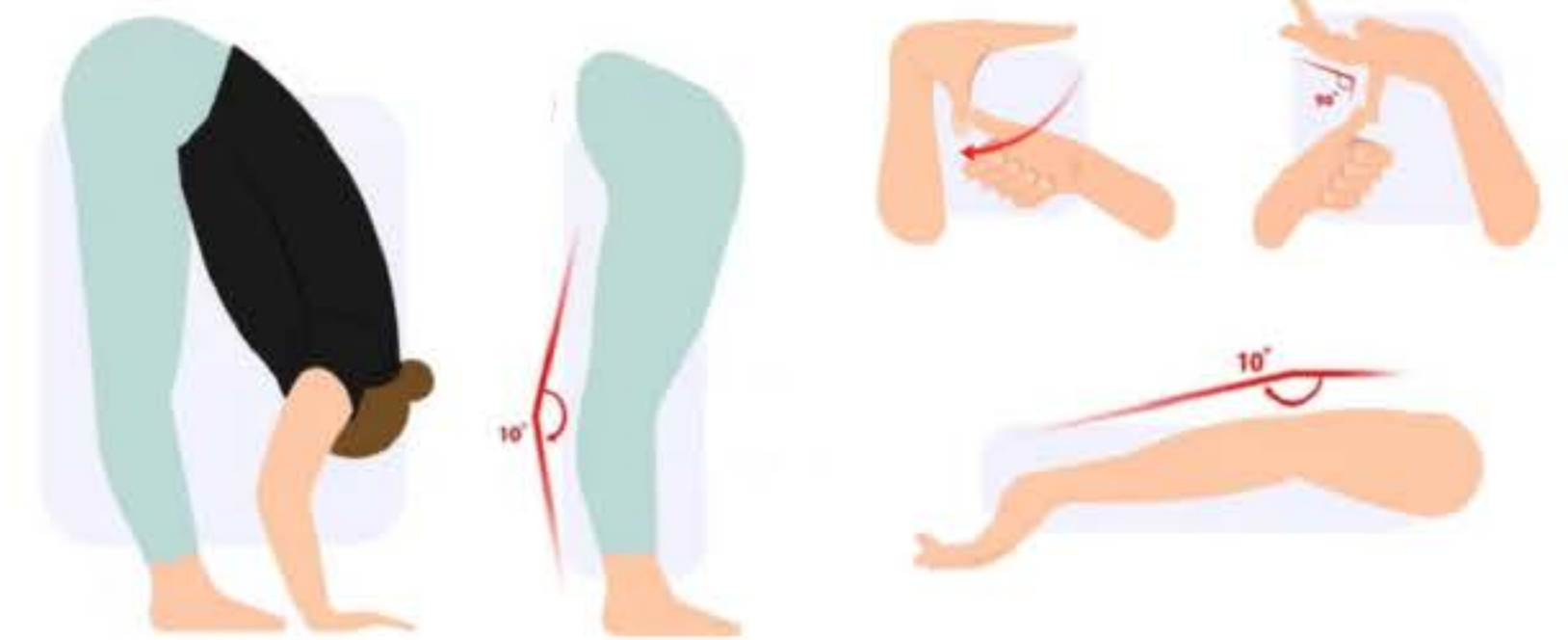


Iron and ferritin status

Note that **coagulation screening is not necessary** at this stage.

Abnormal coagulation tests may be indicative of a bleeding disorder, but most **women with a bleeding disorder have a normal prothrombin time (PT) and activated partial thromboplastin time (aPTT).**

The Beighton score can be used to detect joint hypermobility¹



Easy bruising as a unique bleeding symptom is common in patients with **joint hypermobility**, such as Ehlers-Danlos syndrome. In these patients no specific treatment is required and further bleeding workup is not needed.



In the event of a strong bleeding history, **refer to a haematologist for specialist assessment**, even if the results of general laboratory assessment are normal

FIRST LINE: persistent or recurrent iron deficiency in younger women should prompt consideration of a bleeding disorder



Assessment of iron status, haemoglobin, and red blood cell count is not specific to individual bleeding disorders, but findings provide important information for clinical management¹

- Iron deficiency with or without anaemia is common in women with bleeding disorders — even without anaemia, iron deficiency can be symptomatic and cause, for example, fatigue, muscular weakness, or hair and skin issues, so it must be considered and treated
- Anaemia (haemoglobin <120 g/L)² is also common in women with bleeding disorders



Iron deficiency is best assessed using serum **ferritin and transferrin saturation**^{1,3}

- Low serum ferritin is a strong indication for iron deficiency
- Ferritin can be falsely raised in inflammation and infection
- If serum ferritin is normal ($\geq 15 \mu\text{g/L}$), transferrin saturation (<16%) is helpful to discriminate between truly and artificially normal ferritin with or without iron deficiency
- Serum iron cannot be interpreted in isolation because low values may also be seen in infection and inflammation

World Health Organization definition of iron deficiency²

- Serum ferritin <15 $\mu\text{g/L}$ or
- Transferrin saturation <16% or
- Haemoglobin increase of 1 g/dL after 2 months of iron supplementation (values differ by ethnicity and in pregnancy)



Iron supplementation should be considered once serum ferritin values fall <30 $\mu\text{g/L}$ ⁴

FIRST LINE: start symptomatic treatment, even in the absence of a definite diagnosis

First line treatment is the same for all women with bleeding disorders, so do not hesitate to start therapy to avoid continued or recurrent bleeding symptoms¹



Iron replacement therapy for iron deficiency with or without anaemia²

Oral supplementation (e.g. ferrous sulfate or ferrous fumarate).

Oral iron administration is often poorly tolerated and increases hepcidin levels, thereby decreasing iron absorption from the gut. Therefore, once daily or alternate day rather than more frequent dosing is recommended.³

Rule out gastrointestinal causes of iron deficiency, as appropriate.



Anti-fibrinolytic agent (tranexamic acid) for bleeding symptoms^{4,5}

Tranexamic acid is used for a few days at a time and is not for continuous use.

Clinical experience indicates that patients with regular periods can start tranexamic acid the night before their period to maximise the effect.

Tranexamic acid is contraindicated in patients with

- Severe renal failure (risk of accumulation)
- Haematuria (risk of clot colic)



Hormonal therapy for heavy menstrual bleeding

Combined oral contraceptive or hormonal intrauterine device.

In case of dysmenorrhoea, analgesics can be advised.

Be aware that non-steroidal anti-inflammatory drug (NSAID) use may also interfere with coagulation and may increase bleeding risk, so their use is best reserved until after investigations have been completed.

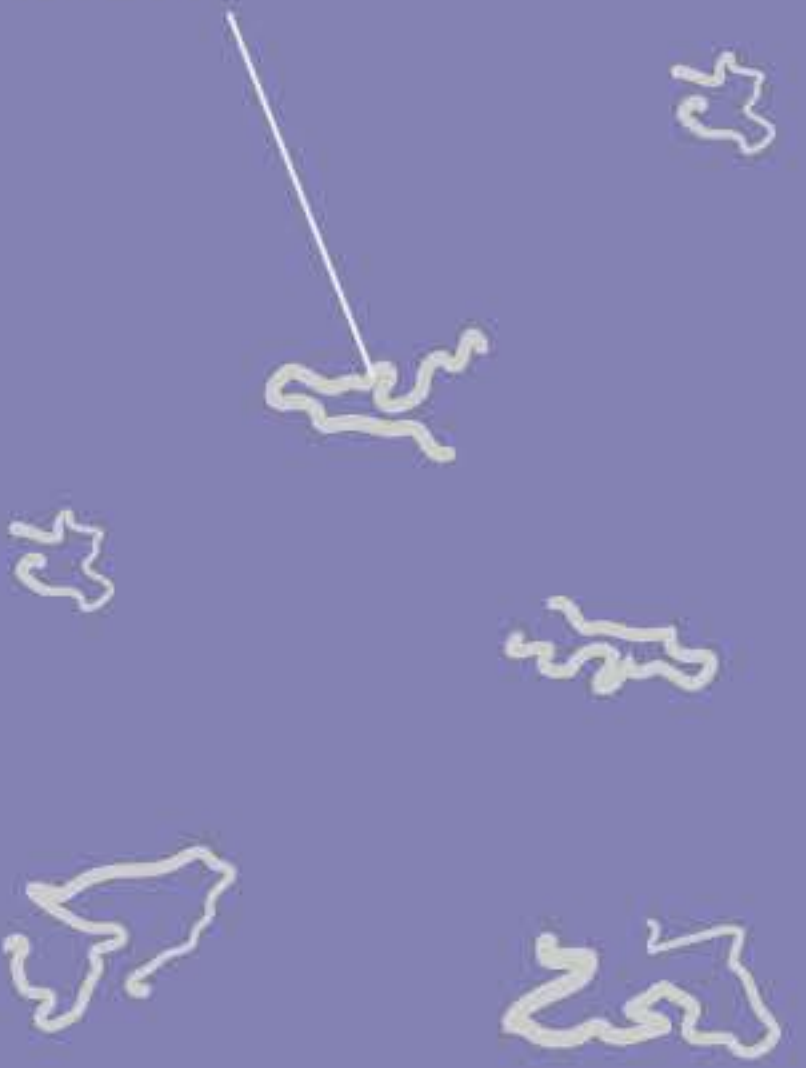
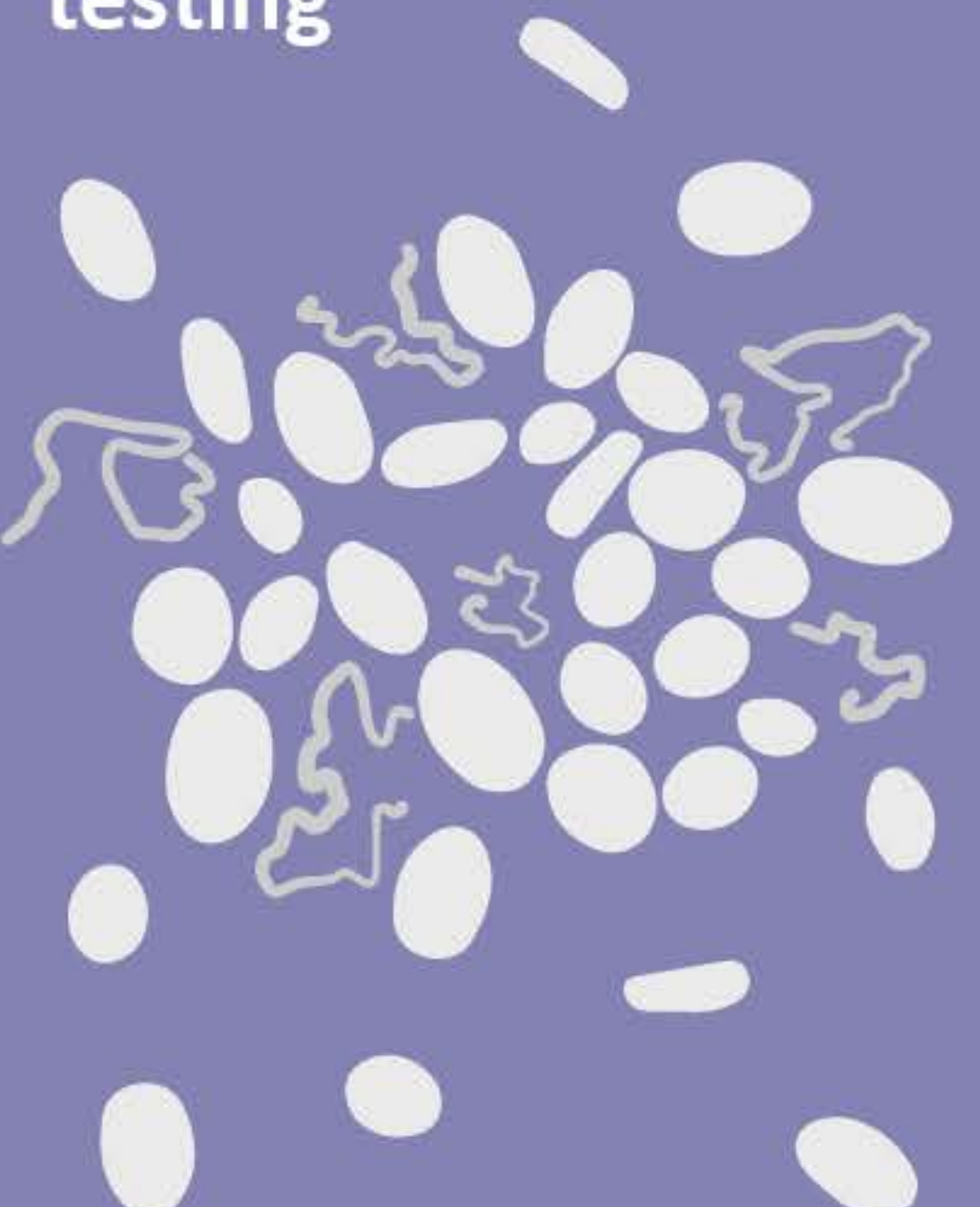

In some women with more severe bleeding symptoms, specialised haemostatic treatment, such as desmopressin, factor concentrates or platelets, may be considered by a haematologist.¹

! Note that patients with severe bleeding should be referred to the Emergency Department for assessment.

1. O'Brien S. Blood. 2018;132:2134-42; 2. Peyrin-Biroulet L, et al. Am J Clin Nutr. 2015;102:1585-94; 3. Munro MG, et al. OBG Management. 2019;31:S1-8; 4. Summary of Product Characteristics. Cyklo-f (tranexamic acid); 5. Chaplin S. J Haem Pract. 2016;3:1-9

SECOND LINE: consult a haematologist for further testing if suspicion of a bleeding disorder is raised by personal bleeding history, family history, and screening tools

Refer to a haematologist for specialist assessment^{1,2}

| | | | |
|---|---|--|---|
| <p>Testing for von Willebrand's disease</p>  | <p>Coagulation testing</p>  | <p>Platelet function testing</p>  | <p>Other testing as appropriate</p> <p>Dietary assessment to assess vitamin C intake³</p> <ul style="list-style-type: none"> ● Vitamin C deficiency, caused for example by fad dieting, can cause bleeding <p>Thyroid function testing⁴</p> <ul style="list-style-type: none"> ● Hypothyroidism can result in heavy menstrual bleeding ● Thyroid function testing is advised only in patients with heavy menstrual bleeding and symptoms suggestive of hypothyroidism |
|---|---|--|---|

1. Hayward CPM. Int J Lab Hematol. 2018;40 Suppl 1:6-14; 2. O'Brien S. Blood. 2018;132:2134-42; 3. Khalife R, et al. Blood Cells Mol Dis. 2019;76:40-4; 4. Demers C, et al. J Obstet Gynaecol Can. 2018;40:e91-103

SECOND LINE: routine coagulation testing can help elucidate the cause of bleeding but is abnormal in only a minority of patients

THERE ARE MANY PITFALLS IN THE INTERPRETATION OF COAGULATION TESTS EXPERT INTERPRETATION IS REQUIRED

Routine coagulation testing includes testing for aPTT and PT

- aPTT provides an evaluation of the intrinsic coagulation pathway: all coagulation factors except factor VII
- PT provides an evaluation of the extrinsic coagulation pathway: mainly factor VII, but also factors V and X, prothrombin (factor II), and fibrinogen (factor I)
- Note that the INR, used to reflect PT in the management of warfarin and hepatology, is not used in bleeding disorders

PT and aPTT are normal in the majority of patients with the most common bleeding disorders (von Willebrand's disease and platelet function defects)

Common causes of prolonged aPTT or PT (or both):

- Medication (the most common cause)
- Reduced nutritional intake or malabsorption
- Systemic disease (e.g. liver disease or connective tissue disease)
- Consumptive coagulopathy (e.g. disseminated intravascular coagulation and fibrinolysis)
- Clotting factor deficiencies (although these should be quite severe, <30% of normal, to cause prolonged PT or aPTT)

Next steps after an abnormal coagulation test:

- Abnormal aPTT: factor-specific assays can be performed, commonly to assess factors VIII, IX, XI, and XII
- Abnormal PT: factor-specific assays for factor VII can be performed

SECOND LINE: testing for von Willebrand's disease is complex and is generally undertaken in specialist haematology centres

Von Willebrand's disease is one of the most common bleeding disorders worldwide, but many people are undiagnosed^{1,2}

- Only ~1/10,000 people are diagnosed with low von Willebrand factor (VWF) or von Willebrand's disease

- ~1/1,000 people have reduced VWF levels and bleeding symptoms

- ~1/100 people have reduced VWF levels

Routine coagulation testing (PT, aPTT) fails to detect low VWF levels or von Willebrand's disease, except in the most severe cases³ — normal PT and aPTT does not exclude this condition

VWF TESTING IS DONE IN SPECIALIST HAEMATOLOGY CENTRES^{1,3}

QUANTITATIVE How much VWF is present

VWF-antigen (VWF:Ag) testing

- VWF levels may be increased by stress, infection, illness, exercise, high-dose hormonal therapy, pregnancy, or trauma
- Blood group also influences VWF levels, which are lower in blood group O than in non-O patients¹

QUALITATIVE How VWF functions

VWF activity assays

VWF activity assays examine the important functions of VWF:

- Platelet binding (VWF:RC_o, VWF:GpIb assays)
- Collagen binding (VWF:CB)
- The ability to carry factor VIII (factor VIII levels)

Expert interpretation of results of these tests and patient history are essential for diagnosis of von Willebrand's disease or low VWF levels

aPTT, activated partial thromboplastin time; CB, collagen binding; GpIb, glycoprotein Ib; PT, prothrombin time; RCo, ristocetin cofactor

1. Leebeek FWG, Eikenboom JC. N Engl J Med. 2016;375:2067-80; 2. Bowman M, et al. J Thromb Haemost. 2010;8:213-6; 3. Ng C, et al. Blood. 2015;125:2029-37

SECOND LINE: platelet count and function should be assessed in all women and girls with a suspected bleeding disorder

Abnormalities of platelet count and function are a common and heterogeneous group of disorders that can result in bleeding symptoms ranging from mild bruising to severe haemorrhage.

Platelet count and function should be assessed in any patient for whom clinical suspicion of an underlying bleeding disorder is high.

PLATELET COUNT¹

- A normal platelet count is not an indication of good platelet function
- Note that the platelet count must fall below 20,000–30,000 mm⁻³ before significant mucocutaneous bleeding occurs
- In most people with platelet function deficits, platelet counts are normal but function is abnormal

PLATELET FUNCTION¹

- Platelet function can be assessed by platelet function tests that expose the patient's platelets to specific triggers to check responses
- Platelet function tests are performed only in specialist centres
- Note that the results of platelet function testing can be influenced by anaemia, blood volume, and intake of specific foods, some dietary supplements, and NSAIDs

Summary & next steps



Bleeding disorders occur as often in women as in men and have a major impact on quality of life, because women experience the additional and frequent bleeding challenges of menstruation and childbirth



If suspicion of a bleeding disorder is raised by personal bleeding history, family history, and screening tools, **perform general laboratory assessment**, including full blood count and iron and ferritin status



First-line treatment is the same for all bleeding disorders, so **do not hesitate to start symptomatic treatment** to avoid continued or recurrent bleeding symptoms, even in the absence of a definite diagnosis. Symptomatic treatment may include iron replacement, anti-fibrinolytic, and hormonal therapy



Contact a haematologist for diagnostic laboratory assessment including coagulation, VWF, and platelet function testing and specialised management

Next steps

Please proceed to the **assessment quiz** to test your knowledge. Visit **Module 1** of this micro e-learning programme to learn more about:

- Recognising signs and symptoms of bleeding disorders in women
- The impact of bleeding disorders on women's quality of life
- How to effectively screen for symptoms of bleeding disorders in women by using the tools available

Note: you will be able to claim your CME credit after passing the assessment quizzes in both Modules 1 and 2



Visit the assessment quiz at www.checkpoint.cor2ed.com



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